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Insulin Resistance and Markers of Inflammation in HIV-Infected Ugandan Children in the CHAPAS 3 Trial

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Abstract

Background: Few studies have investigated metabolic complications in HIV-infected African children and their relation with inflammation.

Methods: We compared baseline and changes in insulin resistance (HOMA-IR) and in markers of inflammation over 48 weeks, in a subset of antiretroviral therapy (ART) naïve Ugandan children from the CHAPAS-3 trial randomized to zidovudine (AZT), stavudine (D4T) or abacavir (ABC) based regimens. Non-parametric methods were used to explore between and within group differences and multivariable analyses to assess associations of HOMA-IR.

Results: 118 children were enrolled; median age (IQR) was 2.8 years (1.7-4.3). Baseline median HOMA-IR (IQR) was 0.49 (0.38, 1.07) and similar between the arms. At week 48, median relative changes in HOMA-IR were 14% (-29%, 97%) in the AZT arm, -1% (-30%, 69%) in the D4T arm, and 6% (-34%, 124%) in the ABC arm ($p \leq 0.03$ for all arms compared to baseline, but p=0.90 for between-group differences). Several inflammation markers significantly decreased in all study arms; sCD14 increased on ABC and did not change in the other two arms. In multivariate analysis, only changes in sCD163 were positively associated with HOMA-IR changes.

Conclusions: In ART naïve Ugandan children, HOMA-IR changed significantly after 48 weeks of ART and correlated with monocyte activation.

Key words: insulin resistance, pediatric HIV, Uganda, treatment –naïve, inflammatory markers, monocyte activation

Cardiovascular and metabolic diseases have become the leading cause of death in HIV-infected individuals[2] and specifically disorders of glucose metabolism and insulin resistance have increasingly been reported in HIV-infected patients[3-7]. HIV-infected children also have a higher prevalence of metabolic disorders compared to the general population[8-10]. Limited longitudinal data also indicate an increased prevalence of insulin resistance in HIV-infected children over time[11,12]. Persistent insulin resistance may increase the lifetime risk of developing type 2 diabetes mellitus[13]. The etiology is likely multifactorial including HIV[18], specific antiretroviral regimen (ART)[19,20] and systemic inflammation[4].

Markers of systemic inflammation have been associated with the development of diabetes and cardiovascular disease in the general population[21-23]. Although ART decreases inflammation and coagulation markers[31,32] levels of inflammatory markers may remain elevated despite virologic suppression. In HIV-infected individuals on ART with good HIV virologic control, markers of systemic inflammation remain higher than in HIV-uninfected individuals[33].

The available limited research evaluating the impact of inflammation in virally suppressed patients has been focused in resource-rich settings and it remains unclear how this relates to pediatric patients in resource-limited settings where the majority of pediatric HIV-infected patients live. Participants from the Children with HIV in Africa-Pharmacokinetics and Adherence/Acceptability of Simple Antiretroviral Regimens (CHAPAS-3) trial who enrolled in Kampala at the Joint Clinical Research Centre (JCRC) present a unique opportunity to examine changes in insulin resistance after ART initation.

METHODS

This was a sub study of the CHAPAS 3 clinical trial (ISRCTN69078957), which was an open randomized phase II/III trial comparing toxicity and efficacy of stavudine (D4T)-, zidovudine

(AZT) - and abacavir (ABC)-based ART among children from Zambia and Uganda[17]. There were four participating sites: University Teaching Hospital, Lusaka, Zambia and Baylor-Uganda Centre of Excellence, Kampala; Joint Clinical Research Centre (JCRC), Kampala and JCRC, Gulu, in Uganda. Caregivers gave written informed consent; older children aware of their HIV status also gave informed assent following national guidelines. The trial was approved by Research Ethics Committees (REC) in Zambia, Uganda and UK. The sub study protocol was also approved by the JCRC REC and the Uganda National Council of Science and Technology.

The primary objectives of CHAPAS 3 were to determine toxicity and pharmacokinetics of the 3 treatment regimens in the pediatric population {Mulenga, 2016 #147}. The sub study presented in this paper focused on the 119 ART naïve children aged 3 months to 4 years that were recruited at JCRC, Kampala.

Study Evaluations

At entry and week 48, fasting (6 hours) blood was obtained for real time measurements of lipid profiles and CD4 count. Blood was processed and plasma stored for batched measurement of HIV-RNA levels. A Material Transfer Agreement, approval from the Uganda National Council of Science and Technology as well as a permit from the Center for Disease Control were approved after which the remainder of the frozen, never previously thawed plasma from the ART naïve children was shipped to Case Medical Center, Cleveland, USA. The plasma samples were used for measurement of glucose, insulin, soluble and cellular markers of monocyte immune activation and markers of systemic inflammation and coagulation. Measurements were performed by the Dahms Research Clinical Unit which is part of the Case Clinical and Translational Science Collaborative of Cleveland (CTSC). Insulin was measured by ELISA sandwich immunoassay (ALPCO, Salem, New Hampshire, USA) and the derived homeostatic

model assessment of insulin resistance (HOMA-IR) was calculated as described[34], where insulin resistance is defined categorically as levels of HOMA-IR greater than 3.16[34,35]

Inflammation, coagulation and soluble immune activation markers

Plasma markers of monocyte activation (sCD14 and sCD163), systemic inflammation (sTNFR1 and 2), oxidized LDL, and fibrinogen were measured. All markers were measured by ELISA (R & D Systems, Minneapolis, Minnesota, USA and ALPCO, Salem, New Hampshire, USA).

Statistical analysis

The primary objective of this analysis was to determine changes in HOMA-IR and markers of inflammation 48 weeks after initiating the randomized treatments and to compare the changes between the groups. Secondary objectives were to determine the association between HOMA-IR and markers of systemic inflammation at baseline with clinically relevant factors and to explore predictors of change in HOMA-IR and changes in markers.

Weight- and height-for-age Z scores were obtained from WHO growth chart standards. Baseline demographics, HIV-related factors, metabolic risk factors and HOMA-IR were described overall and by randomization group using median and interquartile range (IQR) for continuous variables and frequency and percent for categorical variables. Absolute and relative changes from baseline to week 48 were determined. To highlight the magnitude of the observed difference in HOMA-IR after ART initiation. Baseline variables, as well as absolute and relative changes, were compared in the 3 groups with the Kruskal-Wallis test for continuous variables and by the chi-square test or Fisher's exact test, as appropriate for categorical variables. Within group changes were tested using the Wilcoxon matched pairs signed ranks test and Spearman correlations were used to assess associations with HOMA-IR.

Multivariable linear regression was used to model the relative change in HOMA-IR over 48 weeks, with variables with $p<0.1$ in the correlation analysis as well as variables known to affect insulin resistance including age, sex, BMI and family history of diabetes, being candidates for inclusion in the model. Mathematical transformations were used to achieve normality of distribution, as needed. The variance inflation factor (VIF) statistic was used to gauge possible collinearity. Possible departures from normality of residuals and homoescedasticity were evaluated using graphical methods. All analyses were initially performed including all participants and all available data. The results of the analyses including all participants did not differ from the sensitivity analyses performed including only participants with undetectable viral load at week 48; therefore only the former data are presented.

Analyses were performed with SAS9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline Characteristics

Overall, 118 out of 119 ART naïve CHAPAS 3 participants at JCRC, Kampala had stored plasma samples available for HOMA-IR and inflammatory markers measurements and were included in the present analysis. Demographic information and baseline characteristics of the 118 participants are displayed in Table 1; except for viral load which was higher in the D4T arm compared to the ABC arm, all other indices were similar between groups ($p>0.05$). Median age (Q1, Q3) was 2.8 (1.5, 4.3) years; 49% were male. Median weight-for-age Z score was -2 (-3.4, -0.5) and HOMA-IR was 0.49 (0.38, 1.07). A total of 5 participants had HOMA-IR values $\geq$ 3.16. Median absolute and percent CD4+ T cell counts were 867 (648, 1544) cells/mm^3 and 20% (15, 25) respectively. Median viral load was 405,755 (122,250, 1,107,900) copies/mL.

Levels of markers of systemic inflammation and monocyte activation were also similar between groups.

Changes in HOMA-IR after ART Initiation

The relative changes from baseline to week 48 in HOMA-IR are shown in Figure 1. The relative changes in HOMA-IR did not differ between arms, and were a median (Q1, Q3) of 14% (-29%, 97%) in the AZT arm (p=0.03); -1% (-30%, 69%) in the D4T arm (p=0.02); and 6% (-34%, 124%) in the ABC arm (p=0.02). Four additional participants had HOMA-IR values ≥ 3.16 compared to baseline, with no differences between the arms. Within-group percentage changes in HOMA-IR were different from the absolute changes (see Table 2). The absolute changes in HOMA-IR were not significant in any of the arms.

Changes in Inflammatory Biomarkers after ART Initiation

sTNFR1 and 2, and sCD163 all decreased significantly (p<0.05 compared to baseline) within each of the three groups. sTNFR1 decreased by a median (Q1,Q3) 18% (9, 27%) in the AZT arm (p=<0.001), 19% (4, 32%) in the D4T arm (p=0.05) and 18% (3, 30%) in the ABC arm (p<0.001); sTNFR2 decreased by 39% (32, 53%) in the AZT arm (p<0.0001), 32% (30, 56%) in the D4T arm (P<0.0001), 41% (23, 58%) in the ABC arm (p<0.0001); sCD163 decreased by 31% (23%, 47%) in the AZT arm (p<0.0001), 27% (2, 40%) in the D4T arm (p<0.0001) and 20% (7, 45%) in the ABC arm (p=0.02). The changes were not significantly different between groups (p≥0.09). sCD14 did not change in the AZT or D4T arms with median changes of 5% (-12, 19%) in the AZT arm (p=0.14) and median decrease of 0.4% (14, 19%) in the D4T arm (p=0.12). sCD14 increased significantly in the ABC arm by a median of 16% (-0.09%, 33%, p=0.0003). There was no difference in sCD14 between the AZT and D4T arms (p=0.72); however the changes in sCD14 were significantly different between AZT, D4T and the ABC arm

($p<0.05$). Oxidized LDL and fibrinogen did not change significantly within any of the groups and did not differ between groups ($p\geq0.2$). Within-group percentage changes in levels of the inflammatory biomarkers were similar to the absolute changes (Figure 1 and Table 2).

Changes in Other Clinically Relevant Factors after ART Initation

There were significant increases in weight and height in all arms with absolute median changes of weight-for-age Z score of 0.7 (IQR, 0.02, 1.72, $p<0.01$ for all arms); and absolute changes of height-for-age Z score of 0.4 (-0.03, 0.94, $p<0.01$ for all arms). The absolute median change in BMI significantly increased in the AZT arm ($p=0.02$) but not in the D4T or ABC arms ($p\geq0.44$). Total cholesterol, HDL and LDL increased within each of the arms ($p\leq0.03$).

After 48 weeks of ART, 66% of patients had undetectable viral load in the AZT arm, 57% in the D4T arm and 63% in the ABC arm; CD4 percent increased significantly in all arms with absolute median increase of 14% (IQR, 8.5, 19.5, $p<0.01$) for all arms. Insulin did not change at week 48 in any of the arms ($p>0.05$). Except for median glucose that increased significantly only in the AZT arm [62 mg/dL (IQR, 50, 72) at baseline; 69 mg/dL (58, 80); $p=0.03$) at week 48], there were no significant changes between the arms for any of the other clinically relevant factors.

Baseline associations with HOMA-IR and inflammatory markers

At baseline (pre-ART), the only inflammatory marker associated with HOMA-IR was oxidized LDL ($\alpha=-0.20$, $p=0.04$). Oxidized LDL was also negatively associated with weight and positively associated CD4 count. Soluble TNF alpha receptors I and II and sCD14 were negatively associated with weight, age and weight-for-age Z score as well as total and LDL cholesterol. sTNFR1 and 2 were positively associated with absolute CD4 count and viral load, whereas sCD14 was only negatively associated with %CD4 (table 3).

Associations between Changes in HOMA-IR and Changes in Biomarkers

Changes in sCD163 levels were positively associated with changes in HOMA-IR (see table 4). After adjusting for parameters known to affect insulin resistance including age, sex, BMI and family history of diabetes, only changes in sCD163 remained independently associated with changes in HOMA-IR (β coefficient= 0.635, p=0.03).

After 48 weeks of ART, changes in %CD4 count, in weight and LDL cholesterol were negatively associated with changes in sTNFR1 and 2, and in sCD14 ($p< 0.05$). After adjusting for age, sex and LDL, increase in weight remained independently associated with reductions in sTNFR1 and 2(β coefficient= -0.62, $p<0.01$ and β coefficient= -0.42, p=0.05 respectively). Weight also remained independently associated with sCD14 after adjusting for age, sex, viral load and CD4 (β coefficient= -0.63, p=0.02). All VIFs were <2.0.

DISCUSSION

We investigated the effects of 48 weeks of ART in treatment naïve Ugandan children on insulin resistance and markers of inflammation. Data are lacking on the effects of ART on metabolic and inflammatory parameters in African children where the bulk of HIV-infected children reside. We found that in the setting of an NNRTI-based regimen, zidovudine and abacavir increased HOMA-IR and that HOMA-IR is associated with the marker of monocyte activation sCD163.

Insulin resistance is a state in which insulin is associated with an abnormal glucose response and correlates with sequelae such as the development of diabetes[13], cardiovascular disease and malignancies. Although there are no reference values for HOMA-IR in healthy Ugandan children, the baseline HOMA-IR values in our population of underweight HIV-positive Ugandan children were similar to those reported in normal weight HIV-negative European children of

similar age[36] and below 3.16 which has been defined as the cut off for defining insulin resistance in children [35]. The clinical significance of the increase seen in HOMA-IR in the zidovudine and abacavir arms after only 48 weeks is unclear. In addition, it is unknown whether this increase in insulin resistance would translate to important long term consequences in this prepubertal cohort. Other studies have also demonstrated increased insulin resistance in HIV-infected children[9,11,37]. In the study by Chantry et al, participants were either initiating or switching ART regimen[11]. In this particular study, 25% of their patients were three years of age and under, the baseline HOMA-IR value was 0.8 which is similar to our study; however the change seen after 48 weeks was between 0.2-0.8, comparatively larger than the absolute change in our study of -0.01-0.04. However, unlike the participants in our study, these children were on protease inhibitor based therapy which has been linked to insulin resistance in HIV-infected adults[38] and children[39]. Median HOMA-IR values reported by Innes et al in a cross sectional study of HIV-infected children in South Africa were also 0.8 but not different between children on lopinavir and efavirenz based regimens.

A novel finding is the relationship between HOMA-IR and the marker of monocyte activation sCD163 in HIV-infected children. Soluble CD163 has been associated with HOMA-IR in healthy adults and obese children[22,40,41] but to our knowledge no similar correlation has been reported in HIV-infected subjects. sCD163 in HIV-infected adults has been linked with other prevalent and clinically significant co-morbidities in HIV-infection including noncalcified plaque [42] and neurocognitive impairment[43]. Unlike what we have found in our previous study in HIV-infected adults, sTNFα receptors were not significantly correlated with insulin resistance[4]. We may not have been able to detect an association secondary to the small sample size of our study. Another hypothesis that has been proposed by Zanni et al[22], is that TNFα, because of its

short half-life, may not reflect the inflammation in adipose tissues, unlike CD163 expressing macrophages which can gain access to fat cells. Microbial translocation and lipopolysaccharides may play a role in the correlation seen between sCD163 and insulin resistance. Microbial translocation has been well documented in HIV-infected adults[44] and more recently in ART-naïve children in resource limited settings[45]. Markers of microbial translocation have been closely associated with several cardiovascular risk factors including insulin resistance[46,47] and are potent stimulants for release of sCD163 from adipose tissue [48]. We found that after controlling for known demographic characteristics the relationship between sCD163 and HOMA-IR remained statistically significant. These findings suggest that insulin resistance in HIV-infected children may be mediated by immune activation particularly monocyte activation.

Several markers of inflammation (sTNFR1 and 2 and sCD163) decreased significantly after 48 weeks of ART; however, sCD14 did not decrease, and even increased in the ABC arm despite virologic suppression. In addition, oxidized LDL did not significantly change after 48 weeks of ART. Oxidized LDL is a marker of oxidative stress and in adults in uninfected adults has been associated with obesity[27], insulin resistance[28] and cardiovascular disease[29] and in HIV has been associated with markers of immune activation[30]. The lack of change seen in oxidized LDL after 48 weeks of ART may be linked to the lack of change seen in sCD14 as our group has previously shown that plasma levels of oxidized LDL and sCD14 in HIV-infected patients are closely related and oxidized LDL may play a role in monocyte activation[49].

sCD14 contributes to the long term complications seen in HIV and has been linked to subclinical atherosclerosis[50] and overall mortality in HIV[24]. One possible explanation is that Ugandan children are exposed to different pathogens that could impact their intestinal microbiome. In addition, NNRTI-based regimens may not fully suppress viral replication in the

gastrointestinal tract in order to control bacterial translocation. However, similar findings were seen in HIV-infected youth from the United States who were initiated on a protease inhibitor based regimen with tenofovir and lamivudine[51]. In this study, higher levels of sCD14 compared to baseline levels persisted despite 48 weeks of ART and viral suppression. Our group has previously reported on ART-naïve adults randomized to different ART regimens and found that sCD14 decreased only in the integrase inhibitor arms but not with protease inhibitor or NNRTI based regimens[50,52,53]. One of the mechanisms hypothesized is a higher concentration of integrase inhibitor in the enterocytes leading to better control over bacterial translocation[52]. These data suggest HIV-infected Ugandan children even at a young age have increased immune activation and possibly bacterial translocation as measured by sCD14 that do not improve with early viral suppression with NNRTI based regimens.

From a metabolic standpoint, we found that cholesterol, HDL and LDL increased in all arms. Unlike what was seen in ART naïve Ugandan children of similar age enrolled in the ARROW trial, total and HDL cholesterol were not lower in the AZT arm compared to the other two arms[54]. After adjusting for parameters known to affect inflammatory markers, an increase in weight remained associated with reductions in sTNFR1 and 2 and sCD14. This is consistent with data recently presented in HIV-infected adults from the Propsective Evaluation of Antiretrovirals in Resource Limited Settings (PEARLS) trial that found that among HIV-infected persons initiating ART in resource-diverse settings, weight gain among underweight persons had a trend towards lower levels of TNFα- and sCD14 whereas weight gain among obese persons was found to heighten inflammation/immune activation[55]. Our findings suggest that ART initiation among HIV-infected children in resource limited settings, weight gain may reduce

systemic inflammation and immune activation. Another possibility is that inflammation is reduced due to better virologic control and the weight increase is a reflection of return to health.

Strengths of our study include randomized treatment allocation and evaluation of metabolic and inflammatory parameters in a young Ugandan cohort before and after ART initiation. We did not have a comparison group of HIV uninfected children to compare the natural changes seen in insulin resistance in Ugandan children. In addition, we cannot prove causal relationships or exclude the possibility of residual confounding. We focused on a specific population of young HIV-infected Ugandan children whom were underweight at baseline, therefore our findings may not be applicable to other HIV-infected populations.

Author's contributions

GAM and SDF designed the research, wrote the manuscript, assisted with data analysis and obtained funding. VM, GM, AC, JK, CK, NK, DG conducted research (CHAPAS-3 trial team) and reviewed/edited the manuscript. YJ, SD performed the statistical analysis.

Competing Interests

SD sits on the DSMB for clinical trials of Johnson and Johnson. GAM served as a consultant for BMS, Gilead, VIIV, GSK, ICON, Pfizer, and has received research funding from Bristol-Myers Squibb, ViiV, and Gilead.

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Figure 1 Relative change in HOMA-IR and inflammatory markers

Table 1: Baseline demographic, Clinical, HIV related factors and Inflammatory Biomarkers by Arms

	AZT arm N=35	**D4T arm N=42**	**ABC arm N=41**
Age (years)	3.3 (1.7, 4.3)	2.9 (1.8, 3.9)	2.3 (1.5, 3.9)
Male sex	18 (51%)	19(45%)	21(51%)
Weight, kg	10 (8, 14)	11.7 (9, 14)	11 (8, 13)
Height, cm	82 (73.2, 93.6)	85.8 (76.0, 95.4)	80 (72.5, 92.4)
BMI (kg/m^2)	15.6(14.50, 16.53)	15.08(14.46, 17.04)	16.04(15.56,16.79)
Weight-for-age Z score	-2 (-3.4, -1.0)	-1.8 (-3.2, -0.7)	-2.1 (-2.6, -0.5)
Height-for-age Z score	-2.4 (-3.5,-1.1)	-2.6 (-3.3, -1.3)	-2.4 (-3.6, -1.4)
Family History of Diabetes	3 (9%)	3 (7%)	2 (5%)
Glucose level (mg/dL)	62 (50, 72)	63.3 (57, 68)	59.5 (53, 69)
Insulin (uIU/mL)	3 (3, 3.2)	3 (3, 3)	3 (3, 6.8)
HOMA-IR	0.48 (0.38, 0.57)	0.49 (0.43, 0.57)	0.49 (0.41, 1.07)
HOMA-IR ≥3.16	1 (3%)	2(5%)	2 (5%)
Total Cholesterol level, mg/dL	116.6 (99.8, 140.5)	116 (99.4, 146.0)	128.1 (97.7, 152.4)
High-density lipoprotein (mg/dL)	26.3 (18.2, 30.1)	25.9 (19.1, 32.4)	24 (19.8, 34.2)
Low-density lipoprotein (mg/dL)	66 (42.5, 85.8)	66.9 (48.4, 87.7)	67.2 (50.7, 95.5)
Triglycerides (mg/dL)	111 (87.6, 159.9)	102.6 (83.6, 177.2)	114.5 (89.7, 144.1)
Viral load (copies/mL)	401,200 (171,650, 1,079,645)	500,975 (224,805, 1,107,900) [a]	315,090 (122,250, 646,190) [a]
CD4+ T cell counts (cells/mm^3)	925.5 (676, 1505)	864.7 (648, 1236)	810.5 (672, 1544)
CD4+ T cell percent	21 (16, 25)	19.5 (15, 22)	21 (16.5, 24)
sTNFR1 (pg/mL)	1221 (926, 1429)	1249 (993, 1480)	1188 (995, 1572)
sTNFR2 (pg/mL)	5739.5 (4848, 7263)	5851 (4210, 7272)	5478 (4482, 8805)
sCD14 (ng/mL)	1750.5 (1394, 2260)	1778.8 (1578, 2298)	2007.5 (1615, 2308)
sCD163 (ng/mL)	1417.5 (1154, 1588)	1345 (1118, 1533)	1340.3 (970, 1680)
Oxidized LDL (u/L)	140 (64, 263)	122.5 (62, 239)	80 (60, 278)
Fibrinogen (mg/dL)	2008.5 (1783, 2305)	1966 (1664, 2149)	1913 (1647, 2260)

Data are median value (interquartile range) or number (%) of patients.

Abbreviations: AZT, zidovudine; D4T, stavudine; ABC, abacavir; BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; sTNFR1 and 2, soluble tumor necrosis factor alpha receptor 1 and 2; sCD14, soluble CD14; sCD163, soluble CD163.

[a] $p<0.05$ for between group differences

Table 2: Absolute Change between Week 0 and 48 in HOMA-IR and Inflammatory Biomarkers

	AZT arm N=35	P values[a]	D4T arm N=42	P values[a]	ABC arm N=41	P values[a]
HOMA-IR	0.04 (-0.15, 0.32)	0.65	-0.01 (-0.15, 0.3)	0.56	0.03 (-0.25, 0.59)	0.69
sTNFR1 (pg/mL)	-189.5 (-413.5, -93.5)	0.003	-176.5 (-469, -44)	0.002	-223 (-499, -32)	<0.001
sTNFR2 (pg/mL)	-2190 (-3762, -1409)	<0.001	-2335 (-4203, -1228)	<0.001	-2067 (-4358, -1139)	<0.001
sCD14 (ng/mL)	61 (-328.5, 368.3)[b]	0.75	-8 (-280, 490.5) [b]	0.29	284.5 (-17.5, 638.5) [b]	<0.001
sCD163 (ng/mL)	-490 (-665.5, -260.5)	<0.001	-378 (-553.7, -20)	<0.001	-372.7 (-720.5, -103.5)	<0.001
Oxidized LDL (u/L)	-18.5 (-109.5, 18)	0.51	-26 (-98, 54)	0.18	-6 (-154, 113)	0.24
Fibrinogen (mg/dL)	-171 (-553.5, 408.5)	0.20	-82 (-553, 227)	0.65	-75 (-290, 300)	0.96

Data are median value (interquartile range).

[a] For within group differences.[b] $p<0.05$ for between group differences.

Abbreviations: AZT, zidovudine; D4T, stavudine; ABC, abacavir; HOMA-IR, homeostatic model assessment of insulin resistance; sTNFR1 and 2, soluble tumor necrosis factor alpha receptor 1 and 2; sCD14, soluble CD14; sCD163, soluble CD163.

Table 3: Factors univariately associated with HOMA-IR and inflammatory markers at baseline

	sTNFR1		sTNFR2		sCD14		sCD163		Ox-LDL		fibrinogen	
	ρ	**P value**	**ρ**	**P value**	**ρ**	**P value**	**ρ**	**P value**	**ρ**	**P value**	**ρ**	**P value**
HOMA-IR	-0.02	0.82	-0.03	0.73	-0.04	0.64	-0.03	0.72	0.2	0.04	- 0.02	0.87
Age (years)	-0.62	<0.001	-0.66	<0.001	-0.17	0.07	-0.11	0.23	-0.22	0.02	0.05	0.60
Weight-for-age Z score	-0.55	<0.001	-0.49	<0.001	-0.35	<0.001	-0.15	0.10	-0.22	0.02	0.05	0.60
Weight (kg)	-0.69	<0.001	-0.68	<0.001	-0.29	0.002	-0.13	0.16	-0.22	0.02	0.04	0.7
Cholesterol (mg/dL)	-0.26	0.007	-0.26	0.009	-0.21	0.03	-0.03	0.72	-0.02	0.84	0.14	0.15
LDL (mg/dL)	-0.38	<0.001	-0.35	0.003	-0.22	0.02	-0.11	0.26	-0.06	0.55	0.15	0.14
CD4 αbs (cells/mm^3)	0.29	0.002	0.26	0.004	0.03	0.72	0.06	0.55	0.38	<0.001	-0.08	0.40
CD4 %	-0.1	0.28	-0.09	0.35	-0.22	0.02	-0.03	0.75	0.27	0.005	-0.07	0.47
Viral load (copies/mL)	0.248	0.009	0.23	0.01	0.06	0.50	-0.03	0.76	-0.01	0.91	-0.08	0.38

ρ = Spearman correlation coefficient

Abbreviations: HOMA-IR, homeostatic model assessment of insulin resistance; sTNFR1 and 2, soluble tumor necrosis factor alpha receptor 1 and 2; Ox-LDL, oxidized LDL; sCD14, soluble CD14; sCD163, soluble CD163; LDL, low density lipoproteins.

Ox- LDL: oxidized LDL

Table 4: Factors associated with relative change from baseline to week 48 in HOMA-IR

	Univariable Analysis		**Multivariable Analysis**	
	Spearman Correlation	**P value**	**Parameter Estimate**	**P value**
Age (years)			0.003	0.969
Male			-0.375	0.077
Relative Change in BMI (kg/m^2)			0.482	0.649
Family history of diabetes			0.585	0.161
Relative change in sTNFR1	-0.11	0.28		
Relative change in sTNFR2	-0.15	0.13		
Relative change in sCD14	-0.07	0.50		
Relative change in sCD163	0.20	0.04	0.635	0.030

Abbreviations: HOMA-IR, homeostatic model assessment of insulin resistance; sTNFR1 and 2, soluble tumor necrosis factor alpha receptor 1 and 2; BMI, body mass index; sCD14, soluble CD14; sCD163, soluble CD163.